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Research Communications

ATP "potential" of nutrients may regulate plasma corticosteroid concentration: a hypothesis

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Using the cold stressed, fasted animal model, a unified hypothesis is proposed to explain how the ATP "potential" of nutrients may regulate plasma corticosteroid concentration (PCC) by influencing the energy metabolism of the cells, the cellular purine release, and the pituitary–adrenal axis. The nutrient ATP potential is defined as the net number of moles of ATP generated from a mole of nutrient per number of tricarboxylic acid (TCA) cycles used for its metabolism. (J. Nutr. Biochem. 6:12–20, 1995.)

Keywords: corticosteroid; adenosine; urate; ATP; energy; purine; nucleotides

Introduction

In mammals, plasma corticosteroid concentration (PCC) follows a daily circadian rhythm.[1–4] The circadian periodicity of plasma glucocorticoid concentration is dependent on the timing of a meal[5–7] and the nutrient composition of the meal;[8–11] these may exhibit a synchronizing effect on plasma glucocorticoid fluctuations.[2–14] Under normal ambient nonfasted conditions it has been noted that a meal high in protein compared with a starch or fat meal will elicit a much greater increase in PCC.[12] Szabo et al.[9] found that diets that consisted primarily of casein, fat, or carbohydrate had markedly different effects on PCC.[9] Furthermore, these effects were more pronounced in a cold versus thermoneutral or warm climatic environment.[8] Under hypothermic conditions, protein compared with fat or starch diets did not influence plasma corticosteroid levels to the same extent.[8]

Recently, Szabo et al.,[15] demonstrated that not only the main nutrient classes (carbohydrate, fat, protein) but their specific building blocks, i.e., stearic acid and glycerol, can alter PCC to the same relative degree as the parent triglyceride. However, some of the individual components of casein, i.e., leucine, a ketogenic amino acid, versus glutamic acid, a glycogenic amino acid, elicit different effects on PCC.[15] In these studies, the PCC (compared with the values of the fasted-control group) were decreased primarily by nutrients that are energy dense, such as lard and stearic acid. Furthermore, the attenuation of the PCC was not proportional to the energy intake, nor was there a correlation with the caloric content of the specific nutrient(s) fed.

Based on the above cited studies, it is evident that an important relationship exists between nutrients and PCC;[1–13] however, the physiological–biochemical mechanism(s) responsible for these interactions are not understood.

We hypothesize that the energy potential of the nutrients fed regulate extracellular adenosine and/or its metabolic products, and these in turn serve as an agonist of the pituitary–adrenocortical axis.[16–19]

Adenosine and purine release have been shown to be directly related to the energy consumption of the cell, and inversely related to the cell's energy production.[20–22] Therefore, a specific nutrient may alter the cells' energy production and thus alter the extracellular adenosine and purine release which act indirectly through the pituitary–adrenal axis to regulate PCC. However, the caloric content of a gram nutrient is not equivalent to its adenosine triphosphate (ATP) generating potential. For example, the total biological oxidation of 1 M of glutamic acid, leucine, stearic acid, glycerol, or glucose would yield 24.5, 39.5, 148, 22, and 38 ATPs, respectively[23,24]; therefore, 0.149, 0.301, 0.520, 0.238, and 0.211 M ATP can be generated per gram from each of the above nutrients. Although Szabo et al.[15] could not demonstrate a correlation between PCC and the caloric content or ATP/mole of the nutrients fed, they did

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Received June 28, 1993; accepted September 12, 1994.

655 Avenue of the Americas, New York, NY 10010

0955-2863/95/$10.00
SSDI 0955-2863(94)00002-4

find a statistically significant negative correlation between the ATPs generated from a gram of the nutrient fed and the PCC ($r = -0.84$; $P = 0.012$).

Therefore, the purpose of this paper is to present a unifying hypothesis to explain how specific nutrient(s) via their ATP potential may effect purine metabolism and thereby alter PCC.

Materials and methods

Rationale for hypothesis

In order to define the relationships among the cells' nutrient utilization, energy status, and PCC, the net ATP generated from the specific nutrients fed as well as the PCC in the same animals need to be known. Data from our recent publication using a cold stressed-fasted animal model meets this criteria and will be used in subsequent calculations (*Table 1*).[15]

Furthermore, in order to calculate the ATP potential of the nutrients fed and the related changes in PCC the following assumptions are made:

Assumptions related to the cold stressed-fasted animal model

1. There is near maximal negative energy balance.
2. Catabolic pathways are near maximal.
3. Synthetic pathways are minimal.
4. Plasma corticosteroid levels and other catabolic hormones are elevated. The insulin:glucagon (i:g) ratio is low.
5. All of the energy necessary to maintain homeostasis is produced from the nutrients mobilized from the tissue stores.
6. Any dietary nutrient consumed will decrease the energy mobilization from tissue stores in proportion to the net energy generated from the given nutrient plus or minus the metabolic cost of mobilization and absorption of the same quantity of nutrient.
7. Nutrient utilization is directed toward maintenance.

Assumptions made for the stoichiometric calculations, most of which are similar to those presented by Schulz[23] and Atkinson[24,26]

1. All nucleotide triphosphates are interconvertible and can be expressed as ATP.
2. Every metabolic step associated with the conversion of 1 M of ATP to 1 M ADP means a loss of 1 ATP equivalent (Eq); the conversion of ATP to AMP means a loss of 2 ATP Eq.
3. Oxidation of mitochondrial $FADH_2$ and NADH yields 2 and 3 ATPs, respectively.
4. One mole of ATP is required to transfer 1 M of NADH from the cytosol into the mitochondria using the glycerol-phosphate shuttle. The malate-aspartate shuttle does not use ATP. Therefore, depending on the shuttle system used, the NADH generated in the cytosol may yield 2 or 3 ATP Eq.
5. The ATP Eq. of NADPH in the cytosol are not constant. The hexose monophosphate pathway produces 6 M of NADPH at the expense of 0.5 M of glucose-6-P. The ATP equivalent of 0.5 M glucose-6-P is 19.5; therefore, the metabolic price of 1 NADPH may be equal to approximately 3.25 ATPs. If NADH is used to transfer electrons to NADP to form NADPH the process requires 1 M of ATP/M of NADPH.[25] Thus, the metabolic price of 1 M of NADPH may be equal to 3 or 4 ATP Eq depending on the ATP Eq of NADH used. For our calculations, we will use 3 ATP Eq for each NADPH generated by NADP linked to the cytosolic malic enzyme by oxidative decarboxylation of malate and 3.25 ATP Eq for the NADPH produced from the hexose monophosphate pathway.
6. Urea is the only nitrogenous excretory product of protein and amino acid metabolism, and no factor is included in the calculations for the energy cost of urea excretion by the kidney. For urea formation from glutamate and CO_2 the stoichiometric equation proposed by Schulz[23] is used. The overall stoichiometric equation is as follows: Glutamate + 0.5 CO_2 + 0.5 O_2 → 0.5 urea + alpha-ketoglutarate + 0.5 ATP + 0.5 H_2O
7. Since the various nutrients have different molecular weights and carbon numbers, at any given time only a portion of each molecule can undergo an ATP-yielding process. Therefore, the net ATP generated from 1 M of nutrient, in our calculations, will be divided by the number of tricarboxylic acid (TCA) cycles used for the actually ongoing metabolism of that nutrient. The TCA cycle for a particular nutrient serves as a relative time factor for our stoichiometric calculations. Consequently, the ATP potential of a nutrient shall be defined as the net number of moles of ATP generated from a mole of nutrient per number of TCA cycles used for its metabolism.

Results

Stoichiometric calculations

Calculations to determine the ATP potential of leucine, glutamate, and stearic acid are reasonably reliable because the metabolic pathways can be predicted on the basis of well-founded data in the literature. The stoichiometry of the other nutrients (i.e., starch, glycerol, lard, casein, and balanced diet) is much more complicated because several pathways may be ongoing simultaneously. The following calculations are made with these limitations in mind.

Table 1 PCC in cold stressed rats and calculated nutrient ATP potentials*

Nutrients	PCC μg/100 ml M ± SD (Y)	ATP/g nutrient	Stoichiometrically calculated nutrient ATP potentials (X)	Estimated X values*
Fasted	24.16 ± 3.13[a]	0.00	0.00	0.00
Leucine	16.03 ± 3.93[b,c,d]	0.301	12.06	11.92
Glutamate	20.68 ± 7.58[a,b,c]	0.149	5.20	5.15
Stearic acid	12.74 ± 5.31[d]	0.520	16.44	16.72
Starch	15.53 ± 3.29[c,d]	0.211	12.73	12.65
Glycerol	13.32 ± 4.13[d]	0.238	16.00	15.87
Lard	12.01 ± 3.37[d]	—	—	17.78
Casein	22.30 ± 7.06[a,b]	—	—	2.79
Bal. diet	16.95 ± 6.90[a,b,c]	—	—	10.59

Means within columns without common letters differ significantly at $P < 0.05$.
*Calculated on the basis of the following equation: $Y = -0.6863x + 24.2182$.

Leucine is a ketogenic amino acid. Flatt[27] assumes that 0.5 ATP is required for the absorption of 1 M amino acid. The metabolic price for the mobilization of 1 M of amino acid from the tissues can be estimated at 0.2 M of ATP.[28] However, when exogenous amino acid is provided the mobilization cost may be spared; thus, the overall net cost of amino acid absorption would be 0.3 ATP (0.5 ATP for absorption minus 0.2 ATP for mobilization). Exogenous leucine is used primarily for oxidation in 84-hour fasted subjects, as shown by Frexes-Steed et al.[29] This suggests that in our cold-stressed, 72-hour fasted rats, oxidation is the most likely pathway for leucine metabolism. Based on these observations and others,[30,31] the overall metabolic pathway for leucine and its stoichiometry, is depicted in *Figure 1*.

The overall stoichiometric ATP balance for leucine is 36.2 ATP Eq/3 TCA cycles.

ATP potential = 36.2/3 = 12.06 ATP/TCA cycle.

Glutamic acid is a glucogenic amino acid. It is absorbed from the intestine as glutamate. The overall net cost for absorption is 0.3 ATP (the same as leucine). Furthermore, we assume that the rate of oxidative glucose disposal will not be higher than it is in the fasted control animals. The overall metabolic pathway for glutamate and its stoichiometry is based on previously reported studies[32–34] and is depicted in *Figure 2*. Glutamate carbons end up as half a glucose molecule and this glucose is not considered in our calculations because of the low i:g ratio in this group of animals compared with the fasted group (the same assumptions are applied to glycerol utilization).

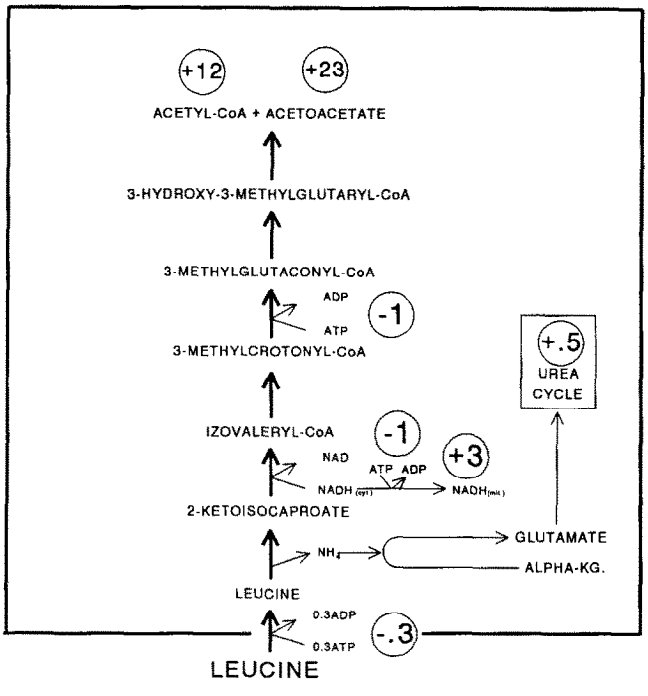

Figure 1 Metabolic pathway for leucine used in stoichiometric calculations of the "nutrient ATP potential." Positive and negative ATP equivalents are represented as the circled values. (cyt.) = cytosolic; (mit.) = mitochondrial; ALPHA-KG = alpha-ketoglutarate.

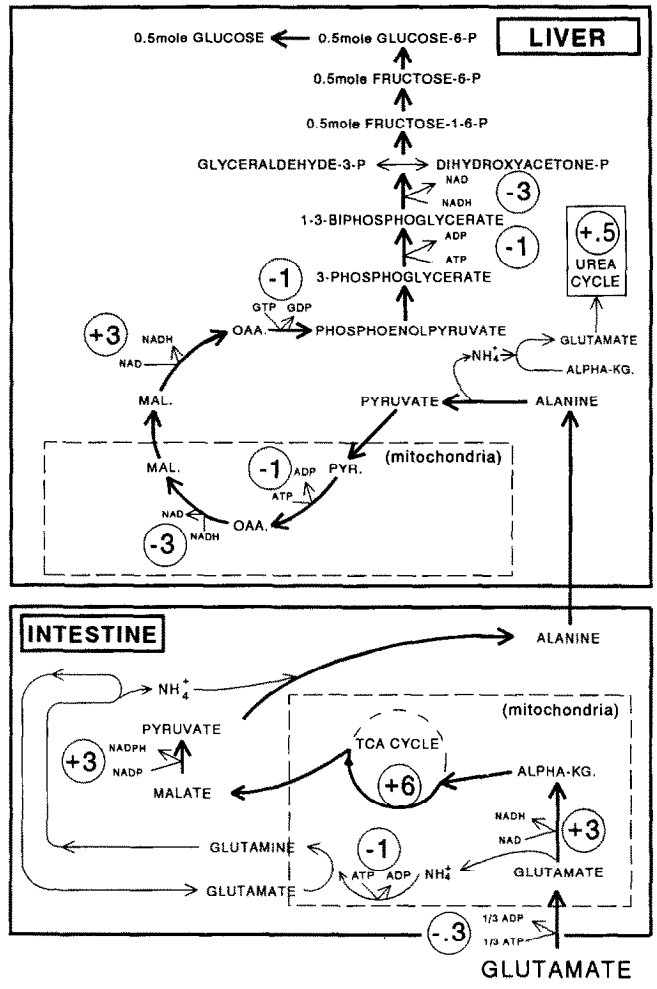

Figure 2 Metabolic pathway for glutamate used in stoichiometric calculations of "nutrient ATP potential." Positive and negative ATP equivalents are represented as the circled values. ALPHA-KG = alpha-ketoglutarate.

The overall stoichiometric ATP balance for glutamate is 5.2 ATP Eq/1 TCA cycle.

ATP potential = 5.2/1 = 5.20 ATP/TCA cycle.

There appears to be no data available related to the cost of absorption or mobilization of *stearic acid*. Therefore, we assume that the cost of fatty acid mobilization from storage sites is close to or equal to the metabolic cost for stearic acid absorption. The net ATP production from the total oxidation of one M of stearic acid yields 148 ATPs/M (40 by 8 beta oxidations, 108 by 9 TCA cycles).

The overall stoichiometric ATP balance for stearic acid is 148 ATP Eq/9 TCA cycles.

ATP potential = 148/9 = 16.44 ATP/TCA cycle.

Since *starch* is hydrolyzed in the small intestine and absorbed as glucose, the stoichiometry of glucose is considered to be equal to that of starch.

Assuming, that (1) the absorption of 1 M of glucose requires 0.5 M ATP,[27] (2) 50% of glycogen is synthesized directly from glucose and 50% of it is derived from glucose via gluconeogenesis,[36–40] and (3) in a unit of time, equal quantities of triose units may be used for oxidation, gluco-

neogenesis, and fatty acid synthesis, given that the i:g ratio is higher than in a fasted group, an appropriate stoichiometry can be calculated as depicted in *Figure 3* (in order to prevent using fractions for the stoichiometric calculations, we started with 50 M of glucose instead of 0.5 M).

The overall stoichiometric ATP balance for starch equals 305.5 ATP Eq/24 TCA cycles.

ATP potential = 305.5/24 = 12.73 ATP/TCA cycle.

Livesey[35] calculated the cytoplasmic ATP equivalent of 1 M glucose to be 25.3. Dividing his value by 2, the numbers of TCA cycles required for its oxidation yields an ATP potential value of 12.65 which is close to our calculated value of 12.73.

Glycerol is a 3-carbon alcohol which can be used as a substrate for glucose and lipid biosynthesis or energy production.[41,42] In dogs, approximately 50% of the glycerol carbon is converted to glucose.[43] With a high glycerol load, glycerol may contribute approximately 50% of the carbon incorporated into glucose.[44,45] On this basis, we assume that in our cold stressed-glycerol fed rats 50% of glycerol carbon is converted to glucose (this glucose is not considered in further calculations because the i:g ratio is lower in this group of animals compared with the fasted group and thus glucose utilization is most likely inhibited), and 50% of the glucose carbons come from sources other than glycerol.[44,45] Therefore, we can assume that 50% of glycerol is oxidized. Our previously reported data[15] also suggest that glycogen synthesis is ongoing in our glycerol-fed, cold-stressed rats. The metabolic pathways and stoichiometric calculations based on the observations above are depicted in *Figure 4*.

The overall stoichiometric ATP balance for glycerol is 16.0 ATP Eq/1 TCA cycle.

ATP potential = 16.0/1 = 16.0 ATP/TCA cycle.

Lard contains mainly long-chain fatty acids and glycerol. Therefore, its ATP potential is most likely close to the value derived for stearic acid (16.44) and/or glycerol (16.0).

Since *casein* is composed of 20 different amino acids and the *balanced diet* contains casein, starch, and lard, the synthetic and catabolic pathways which are ongoing simultaneously cannot be estimated accurately. Therefore, the stoichiometry of casein and the balanced diet will not be directly calculated.

Discussion

Since we noted a statistically significant correlation between the PCC and the ATP-generating capacity of a gram nutrient fed ($r = -0.845$, $P < 0.05$), it is not surprising that the PCC levels of the dietary groups are correlated with the stoichiometrically calculated ATP potentials of the nutrients ($r = 0.999$, $P < 0.0001$) (*Figure 5*). The highly significant correlation between the nutrient ATP potentials (the net number of ATPs generated from a mol nutrient divided by the number(s) of TCA cycle(s) used for its metabolism suggests that the ATP potential of the specific nutrients may be a predictor of the PCC. Using the equation $Y = -0.6863X + 24.2182$, which is derived from the stoichiometrically calculated nutrient ATP potentials and PCC (see *Figure 5*), we can then estimate the ATP potentials of the more complex nutrients e.g., lard, casein, and the balanced diet based on PCC of the animals fed these diets (*Table 1*).

Therefore, we conclude that there exists a relationship between the PCC of cold stressed rats and the ATP potential of the specific nutrients fed.

Our ATP potential hypothesis indicates that stress may be interpreted as an energy (ATP) shortage in the organism. We suggest that a feedback control mechanism exists between the pituitary–adrenal axis and the energy metabolism of the cells. We hypothesize that changes in extracellular purine(s) concentration act as messengers for communicating the energy status of the peripheral cells and tissues to the pituitary–adrenal axis (*Figure 6*). The following evidence supports this hypothesis.

1. The activity of the key enzymes (5′-nucleotidase, adenylate deaminase) responsible for degradation of AMP and consequently for adenosine and purine release, are controlled by the adenylate energy charge of cells.[46–49] It is the incurred temporary or persistent energy deficit, i.e., the difference between acute energy production and actual energy utilization, which appears to be the key element.[50]
2. In a study using graded hypoxia, adenosine release rose with falling phosphorylation potential ([ATP]/[ADP][Pi]), energy charge ([ATP] + 1/2[ADP])/([ATP] + [ADP] + [AMP]), and an increase in [AMP].[51]
3. Adenosine formation[20,21] and purine release are directly related to the rate of energy consumption, and inversely related to the rate of energy production, in the isolated heart.[22]
4. In vivo, intraperitoneally administered adenosine and adenine nucleotides increased PCC[16–19] and in a dose-dependent manner.[17,19]
5. Added in vitro, adenosine reduced both adrenal basal and ACTH stimulated corticosterone release,[17] suggesting that the in vivo PCC effect observed by others[16,18,19] is centrally mediated.
6. Adenosine-influenced adenylate cyclase activity in cultured anterior pituitary cells,[52] and via two different types of receptors (A1 and A2), regulated the accumulation of cyclic AMP in cultured brain cells.[53,54]
7. Adenosine stimulated the release of ACTH from cultured anterior pituitary cells[55] and anterior pituitary quarters[17] in vitro.
8. Intraperitoneally administered urate, the end product of adenosine catabolism, increased PCC as well as adenosine in a dose-dependent manner.[19]
9. Calculations based on the data of Filteau et al.,[66] show that URA accumulation in the hypothalamus of mice is directly correlated with PCC ($r = 0.83$).
10. Corticosterone possesses two distinctly opposite metabolic actions (anabolic at low and catabolic at high plasma concentrations), which are strictly dose-dependent and linked to type I and type II corticosteroid receptor binding.[56]
11. Glucocorticoid receptor activation leads to up-regulation of adenosine A1 receptors and down-regulation of adenosine A2 responses.[57]

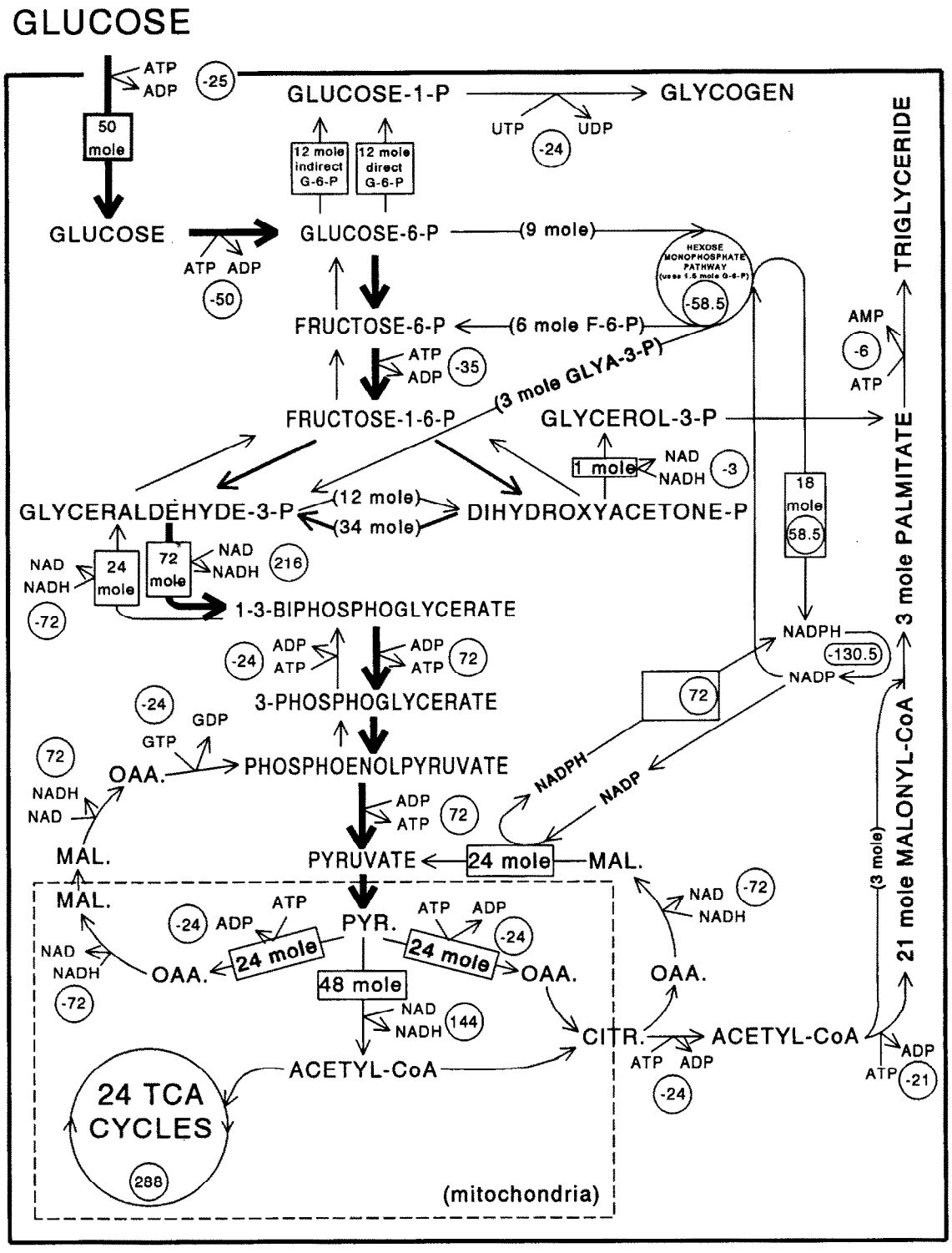

Figure 3 Metabolic pathway for glucose used in stoichiometric calculations of the "nutrient ATP potential." Positive and negative ATP equivalents are represented as the circled values. G-6-P = glucose-6-phosphate; PYR = pyruvate; OAA = oxaloacetate; MAL = malate; CITR = citrate; GLYA-3-P = glyceraldehyde-3-phosphate.

These studies together with our proposed hypothesis suggest a close relationship between the ATP potential of nutrients and PCC as summarized in *Figure 6*.

As shown in *Figure 6*, the net ATPs generated from a nutrient may influence the energy status of the cells (the cytosolic [ATP]/[ADP][Pi] ratio). The cytosolic [ATP]/[ADP][Pi] ratio is the chemical potential that drives ATP-consuming reactions and also regulates respiratory rate.[58]

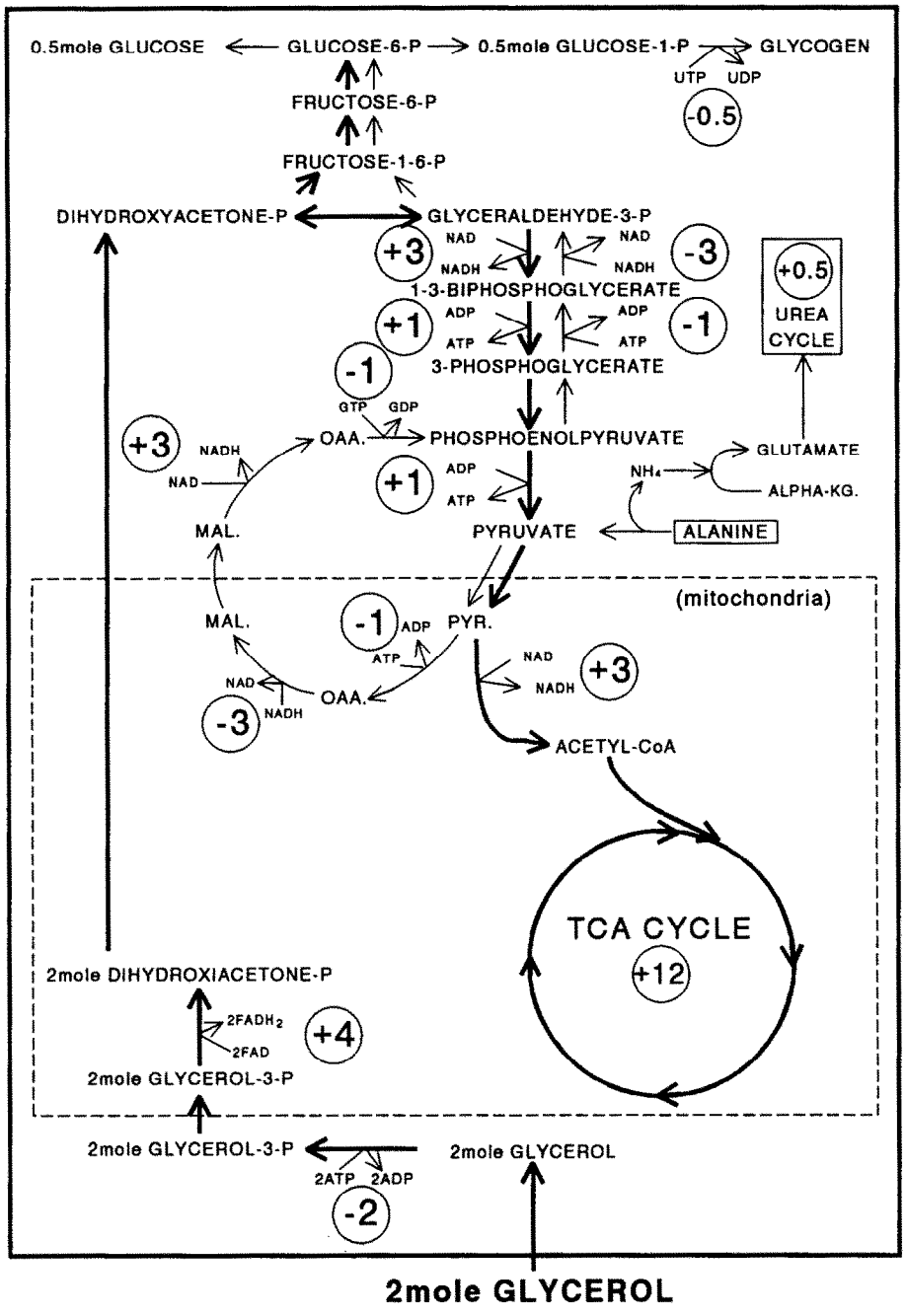

Figure 4 Metabolic pathway for glycerol used in stoichiometric calculation of the "nutrient ATP potential." Positive and negative ATP equivalents are represented as the circled values. ALPHA-KG = alpha-ketoglutarate.

The cytosolic adenylate energy charge appears to control the activity of the enzymes responsible for adenosine release[46–49] and perhaps its further catabolism to urate.

The changes in plasma purine concentration may influence pituitary ACTH secretion through purine receptors, which are coupled to the adenylate cyclase-cAMP system.[52–54]

During metabolic stress energy shortage, nucleotide catabolism and purine release are increased. The high extracellular purine concentration may activate the adenylate cyclase cAMP system in the anterior pituitary via the P1A2 purine receptors and increase ACTH secretion and plasma concentration which stimulate adrenal glucocorticoid secretion. Uric acid, the end-product of adenosine catabolism, also increases PCC in a dose-dependent manner,[19] which may suggest that uric acid can also be a signal carrier between peripheral metabolism and the hypothalamo–pituitary–adrenal system.

The increased PCC through type II glucocorticoid receptors activates protein catabolism and amino acid release[56,59–61] from the storage sites for catabolic energy-yielding reactions. The ATP generated from the mobilized

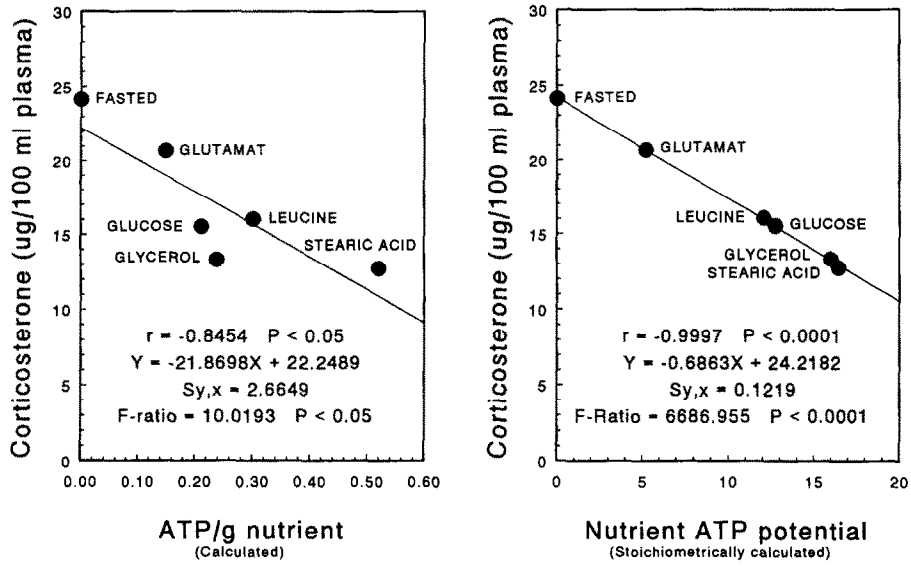

Figure 5 Correlation coefficient between PCC and nutrient ATP.

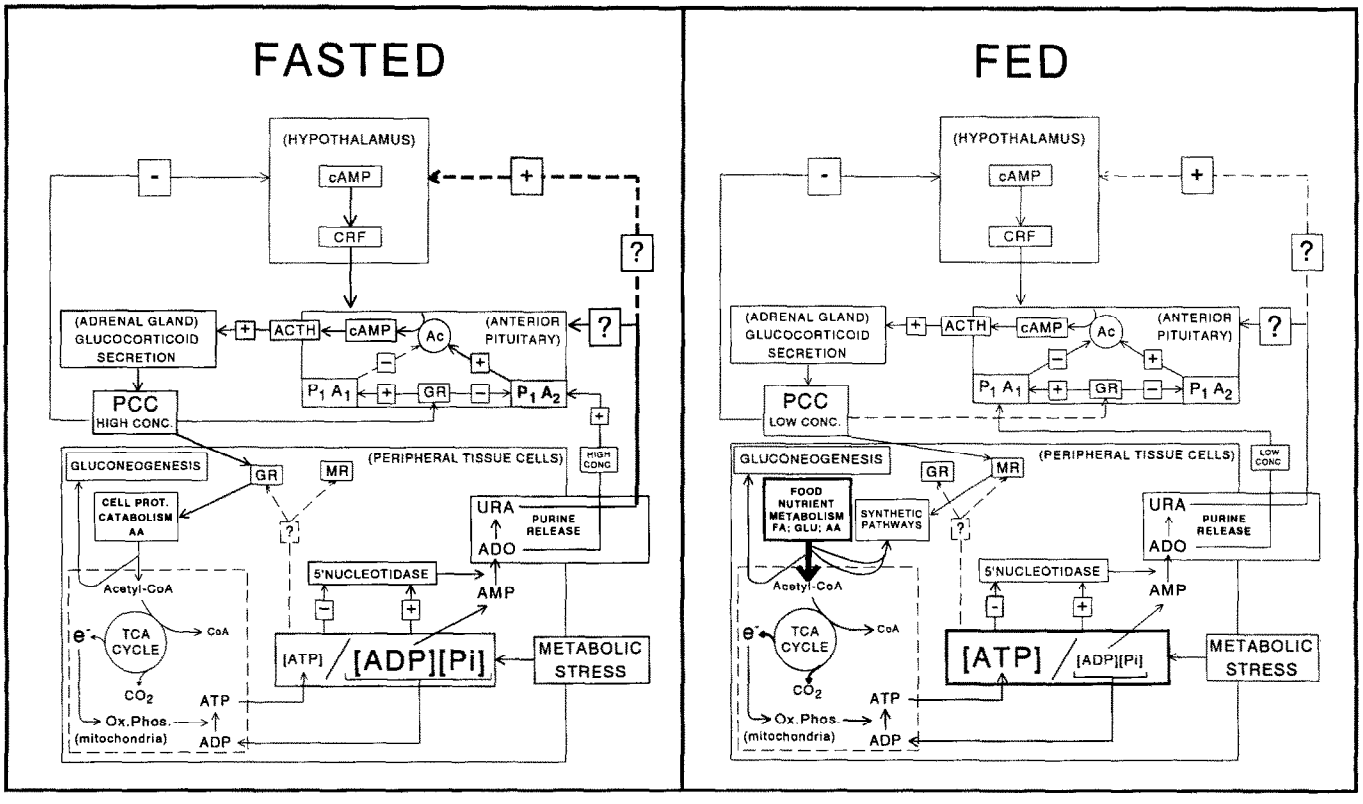

Figure 6 Proposed feedback control mechanism for nutrient-PCC interaction. CRF = corticotropin-releasing factor; Ac = adenylate cyclase; cAMP = cyclic AMP; P1A1 & P1A2 = purine receptors; ADO = adenosine; URA = uric acid; FA = fatty acids; GLU = glucose; AA = amino acids; GR = Type II or glucocorticoid receptor; MR = Type I or mineralocorticoid receptor; PCC = plasma corticosteroid concentration; Ox.Phos. = oxidative phosphorylation.

nutrients will increase the cytoplasmic phosphorylation potential and adenylate energy charge and thereby decrease the adenosine and purine release which will diminish PCC via the above cited mechanisms.

The actual mechanism(s) is probably much more complicated, and other feedback control mechanisms, including the purine and glucocorticoid receptors, may be involved as indicated in *Figure 6*. The regulation of receptor synthesis

and or activation may also be under the control of cytoplasmic ATP concentration.[62–65] However, as predicted by our hypothesis, it appears that under controlled metabolic stress, i.e., cold stress and starvation, there is a direct relationship between the ATP potential of a given nutrient and the observed change in PCC. We acknowledge that these assumptions may apply only to animals in a cold stressed fasted state.

A comprehensive summary of the literature concerning all aspects of the feed back control mechanism(s) of the pituitary–adrenal axis is beyond the scope of this paper. However, our hypothesis helps to clarify the role of nutrients, their ATP potential, and the interrelationship between the pituitary–adrenal axis.

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